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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,344	01/19/2001	Neil T. Parkin	59597-D/JPW/CMR	7661

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	16

DATE MAILED: 01/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/766,344	Applicant(s) PARKIN ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *98-112,114-117 and 121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98-112,114-117 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

In the preliminary amendment in paper no. 9, applicant cancelled claims 1-97, 113, 118-120, and 122. Claims under consideration are: 98-112, 114-117, and 121.

Priority

If applicant desires priority under 35 U.S.C. 119(e) and 120 based upon a previously filed copending applications 60/140483 and 09/591899, respectively, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date

the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country. Since international application is PCT/US00/17178, filed June 22, 2000 is a continuation of 09/591899, applicant may also be eligible to claim priority to the foreign application.

Drawings

The drawings are objected to because a description of individual figures 3a-3e, 4a-4e, and 5a-5e must be in the paragraph description under the Brief Description of the Drawings section. Also, Figure O is not labeled in the drawing and there is no brief description for Figures P and Q in the specification. It is also noted that Figures 6 and 7 appear in pages 152 and 153 of the specification, respectively, but there is no description for these figures in the Brief Description of the Drawings section.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. An example is found on page 8, lines 14 and 15. Applicant is

required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Also, the numbers highlighted in black in Tables 1 and 2 on pages 154 and 155, respectively, are hard to read.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 107 is objected to because "48" is listed twice in line 3. Claim 116 is objected to because "mutation" should be plural. Claim 117 is objected to because "46" is listed twice in lines 5 and 6.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 98-112, 114-117, and 121 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims do not clearly state what is intended in the methods and the claims are replete with a lack of antecedent basis.

Claims 98-112 and 114-117 are unclear because it cannot be determined if the intent is really a two-step assay, involving a sequence determination followed by a drug sensitivity test, or if the intent really a one-step assay where the sequence at the recited codon is used to indicate

drug sensitivity. If a two-step assay is truly intended, what is the point of evaluating the nucleic acid sequence, since the drug sensitivity test alone will accomplish the stated purpose of the assay? The claims (101-107, 110-112) are drawn to determining whether something (presumably a sample from an HIV-infected person) has certain mutations at specific codons that determine a change in susceptibility to certain protease inhibitors. The claims state that the change in susceptibility is a decrease or increase in susceptibility to certain drugs. Is the intended meaning of the claims directed to determining whether mutations at specific codon combinations lead to a decrease or in susceptibility to a drug, or do the instant mutation combinations actually denote a decrease or increase in susceptibility?

Claim 121 is unclear because it cannot be discerned if the mutation in codon 82 or 90 is part of the patient-derived segment, or if it is in addition to the patient-derived segment? Also, what is the resistance test vector resistant to? Is the indicator gene indicating the expression of the patient derived segment, or is indicator gene intended to identify resistance to something?

Claim 100 recites the limitation "protease inhibitor" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 101-107 and 110-112 recite, "...having a mutation..." in line 1. It is presumed that the substance having a mutation is an HIV protease in a patient's sample. However, since the claims do not specifically state what has a mutation, the claim is vague and indefinite. Also, there is a lack of antecedent basis in the claims for any mutation.

Claim 102 recites the limitation "step (c)" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 103 recites the limitation "step (c)" in lines 4 and 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 104 recites the limitation "having a mutation at codon 90...74" in lines 1-3. There is insufficient antecedent basis for this limitation in the claim.

Claim 105 recites the limitation " step (c)" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 106 recites the limitation " step (c)" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 107 recites the limitations starting with "having a mutation at codon 82...93" in lines 1-7. There is also a lack of antecedent basis for a secondary mutation at codon 46 when the primary mutation is at codon 82 and for a secondary mutation at codon 77 when the primary mutation is at codon 90. There is insufficient antecedent basis for any of the limitations in the claim.

Claim 108 recites the limitation "protease inhibitor" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 109 recites the limitation " step (c)" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claim is also unclear because the claim states that susceptibility is greater than ten fold, which is compared to what?

Claim 110 recites the limitations "having a mutation at codon 82...54" in lines 1-6. There is insufficient antecedent basis for these limitations in the claim.

Claim 111 recites the limitations " having a mutation at codon 82...susceptibility" in lines 1-5. There is also a lack of antecedent basis for a secondary mutation at codon 46 when the

primary mutation is at codon 82 and for a secondary mutation at codon 77 when the primary mutation is at codon 90. There is insufficient antecedent basis for these limitations in the claim.

Claim 112 recites the limitation " having a mutation at codon 82...susceptibility" in lines 1-8. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 98-112 and 114-117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining whether or not some mutations at certain codons lead to an increase or decrease in resistance to certain protease inhibitors, does not reasonably provide enablement for some existent mutations at certain codons (i.e. codon 90) to denote an increase or decrease in drug resistance to a specific protease inhibitor or for the lack of mutations to indicate an increase in drug resistance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

As discussed above, it cannot be determined from the claim language whether the intent of the claims is drawn to determining whether mutations lead to an increase or decrease in drug sensitivity or whether the claims are drawn to certain mutations denoting an increase or decrease in drug susceptibility. The specification teaches that a mutation at codon 90 is a poor indicator for determining drug susceptibility; see page 178, lines 26-28. There is no teaching in the prior art that teaches a way to predict which codon mutations would indicate drug resistance and the specification supports this inability in teaching that a mutation at codon 90 cannot determine

drug resistance. The specification does not describe the nature or characteristics of a codon mutation that would indicate resistance to a specific protease inhibitor therapy. Therefore, due to the lack of predictability in the art to predict which codon mutations indicate drug resistance, the lack of teaching in the specification for predicting which mutations lead to drug resistance, the inability of the skilled artisan to immediately identify a codon mutation that indicates drug resistance, it is determined that an undue quantity of experimentation would be required of the skilled artisan to predict which drugs a patient will be resistant to based analyzing the codon sequence.

In addition, the specification teaches that an absence of specific mutations at certain recited codons lead to a decrease in susceptibility, i.e., no mutations in a sample leads to drug resistance, see for example page 180, lines 5-7 and 26-28 and page 181, lines 18-20. In other words, according to the teachings in the specification, if mutations were found at the recited codons in the claims, there would be a decrease in drug resistance and the protease inhibitor therapy would be effective and if there were no mutations found, the protease inhibitor therapy would not be effective because of an increase in drug resistance. The skilled artisan would conclude that the presence of mutations indicates drug resistance (or a decrease in susceptibility), not a decrease in drug resistance. Also, the codon mutation combinations in claims drawn to an increase in susceptibility (103, 106, 111), i.e. not drug resistant, are shown to be drug resistant in the art, see codon mutations Table 1 of Young et al. (The Journal of Infectious Diseases. Nov. 1998; 178(5): 1497-501). Young et al. teaches that mutations occurring at codon 90 and 48 or 90 and 93 and 82 or 46 correlate with increased resistance to saquinavir and mutations in codons 90 and 84 correlate with increased resistance to indinavir. Young et al. teaches that specific

mutations at certain codons are associated with drug resistance, not that the absence of mutations confers drug resistance. Therefore, the skilled artisan would predict that a sample devoid of any codon mutations would be more susceptible to drug treatment. The specification also teaches that the presence, not the absence of some codon mutations in Table 16 are positively correlated with sensitivity to saquinavir, which is the opposite of what is claimed in claims 102, 105, and 110-112. Due to the ambiguity of the claims, the knowledge of the skilled artisan and the state of the art that indicate that certain codon mutations are associated with drug resistance, it is determined that an undue quantity of experimentation would be required of the skilled artisan to make or use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 98-102, 104, 105, 107, 108, 110, 112, and 114-116 are rejected under 35 U.S.C. 102(b) as being anticipated by Young et al. (The Journal of Infectious Diseases. Nov. 1998; 178(5): 1497-501).

The claims are drawn to a method of assessing the effectiveness of protease antiviral therapy by collecting a sample from an HIV-infected person, evaluating whether the sample has a nucleic acid encoding a mutation at codon 82 (A, F, S, or T) or L90M, and as well as specific secondary mutations, and determining the change (increase) in susceptibility (i.e., drug resistant) to indinavir, saquinavir, and/or amprenavir.

Young et al. teaches a method of assessing the effectiveness of protease antiviral therapy by collecting plasma and peripheral blood mononuclear cells from an HIV-infected person, evaluating whether the sample has a nucleic acid encoding a mutation at codon 82 (A, T, or F) L90M, and as well as specific secondary mutations, and determining the change in susceptibility to indinavir, saquinavir, and/or amprenavir, see the abstract, the methods section on page 1497, and Table 1 on page 1498. Table 1 of Young et al. summarizes the resistance patterns of codon mutations for drug resistance on page 1498. Young et al. teaches mutations at codons 90 and 84 lead to increased resistance to saquinavir and indinavir. Young et al. also teaches that codon mutations in codons 90, 84, 82, 46, 10, and 54 correlates to an increase in sensitivity to indinavir and saquinavir. Therefore, the teachings of Young et al. anticipate claims 98-102, 104, 105, 107, 108, 110, 112, and 114-116.

Claims 98-100 and 107-109 are rejected under 35 U.S.C. 102(b) as being anticipated by Hertogs et al. (Antimicrob. Agents Chemother. Feb. 1998; 42(2): 269-276).

Hertogs et al. teaches a method of assessing the effectiveness of antiviral therapy by collecting blood samples from an HIV-infected person by collecting a sample, determining the genotype of each sample, evaluating susceptibility to specific protease inhibitors, and determining the fold increase, which was greater than 10 fold in some instances, see page 270 and Tables 5 and 6 on page 274. Hertogs et al. also teaches that mutations at codons 90 and 93 lead to correlate with drug resistance to indinavir and saquinavir, anticipating claims 98-100 and 107-109.

Claim Rejections - 35 USC § 102

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim117 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Young et al. or Hertogs et al. in the alternative, *supra.*

The claim is drawn to a method of assessing the effectiveness of protease therapy in a patient by collecting a sample from an HIV-infected patient, evaluating whether or not there is a mutation in codons 82 and 90, and other specific secondary mutations, and determining susceptibility change to amprenavir.

Young et al. or Hertogs et al. teach a method of assessing the effectiveness of protease therapy in a patient by collecting a sample from an HIV-infected patient, evaluating whether or not there is a mutation in codons 82 and 90, and other secondary mutations, and determining susceptibility change to amprenavir, see Table 1 on page 1498 of Young et al. or Table 6 on page 274 of Hertogs et al. Although Young et al. or Hertogs et al do not specifically teach evaluating each of the recited mutations in the claim, the references teache evaluating sequences derived from patient plasma and blood mononuclear cells, which would comprise all of the mutations recited. Therefore, it is concluded that Young et al. or Hertogs et al. evaluate all possible mutations in the claims to determine resistance to amprenavir. Therefore, the teachings of Young et al. or Hertogs et al. render the invention obvious, if not anticipated.

Claim 121 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hertogs et al. as applied to claims 98-100 and 107-109 above, and further in view of Capon et al. (US 5,837,464).

The claim is drawn to a resistance test vector comprising a patient-derived segment comprising a nucleic acid having specific mutations and an indicator gene, wherein the indicator gene is dependent on the expression of the patient-derived segment.

See the teachings of Hertogs et al. above. Hertogs et al. does not teach a resistance test vector.

However, Capon et al. does, see claims 30-34, 37, 38, 45-47. One of ordinary skill in the art at the time the invention was made would have been motivated to express a patient-derived segment into a resistance test vector to amplify the genes that contain drug-resistant mutations so as not to deplete the primary source derived directly from the patient. One of ordinary skill would be further motivated to express patient-derived segments into a test vector to simultaneously test different segments that may not be adjacent in the genome and spare the time and expense of generating recombinant viruses expressing mutations. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Capon et al. teaches introducing the test vector into host cells to determine drug resistance mutations, see claim 46, and Hertogs et al. teaches determining the presence of drug resistance by transforming recombinant viruses in tissue culture in the presence of drugs. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
January 12, 2002

James C. Housel
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